Title: Impact of Positive Margin Re-excision on Median 5-Year Follow-Up Results in an International Single Arm Prospective Trial Evaluating Early-Stage Breast Cancer Patients Treated with Intra-Operative Electronic Brachytherapy

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Purpose: ASTRO APBI Consensus Statements define three ("Unsuitable", Cautionary", "Unsuitable') categories for breast cancer patients considering off-trial APBI treatment, with positive margins being an unsuitable criteria.[1,2] TARGIT-A recommends patients with positive margins receive whole breast radiation therapy (WBXT).[3] Treatment and outcomes of early-stage breast cancer patients having positive margins following intra-operative radiation therapy (IORT) using electronic brachytherapy in a single arm prospective trial, although not a pre-specified subset, is analyzed in this report.

Methods: Patients(women ≥40 years, invasive ductal carcinoma [IDC] or ductal carcinoma in situ [DCIS], single lesion ≤3cm, no lymphovascular invasion/extensive intraductal component, cN0, no neo-adjuvant therapy) were enrolled in a single arm prospective multi-institution trial designed to determine the efficacy and outcome of single fraction 20 Gy IORT using disposable balloon electronic brachytherapy following lumpectomy. Subjects were grouped into "Suitable"(patients ≥50 years, size ≤2cm, Tis/T1, negative margins, unicentricity, pN0, IDC, low/intermediate grade DCIS ≤2.5cm), "Cautionary"(patients 40-49 years, size 2.1–3cm, invasive lobular carcinoma, DCIS ≤3cm) and "Unsuitable"(size >3cm, positive margin, multicentricity, pN+) categories after treatment. "Unsuitable" patients with positive margins (defined as ink on tumor) were allowed one re-excision to negative margins before receiving WBXT recommendations. Demographics, histopathology, treatment, ipsilateral breast tumor recurrences (IBTR) (recurrence in the lumpectomy cavity/index quadrant), and survival were extracted from chart reviews. MEDRIO was used for data compilation and statistical analysis. IBTR at median 5-year follow-up in "Unsuitable" patients having positive margins was the primary focus of this analysis.

Results: Between 2012-2018, 1199 subjects successfully treated at 26 international institutions per protocol were categorized as "Suitable" (890 patients), "Cautionary " (187 patients), and "Unsuitable" (122 patients). At median 5-year follow-up, there were 42(3.50%,95%CI=2.5,4.5) IBTR with 25(2.8%,95%CI=1.7,3.9) in "Suitable", 12(6.4%,95%CI=2.9,9.9) in "Cautionary", and 5(4.1%,95%CI=0.6,7.6) in "Unsuitable" categories. Treatment of "Unsuitable" patients with positive margins is summarized in Table 1. 72 of the 93 patients having positive margins were re-excised, 70 obtaining negative margins. One patient with persistent positive margins was treated with WBXT, another chose mastectomy. There were four IBTR in this group. 21 patients refused re-

excision (one IBTR). Twelve patients received WBXT (no IBTR). The one breast cancer-related death did not have positive margins. Patients with positive margins had an increased IBTR (5.4%) compared to patients with negative margins (3.3%), which was not statistically significant (p=0.307), with an odds ratio of 1.69(95%CI=0.65,4.40).

Table 1. Treatment of “Unsuitable” patients with positive margins

TREATMENT	**PATIENTS**
IORT, (+) margins, re-excision	54
IORT, (+) margins, re-excision, WBXT	10
IORT, (+) margins, no re-excision	16
IORT, (+) margins, no re-excision, WBXT	5
IORT, (+) margins, mastectomy	6
IORT, (+) margins, re-excision, WBXT, mastectomy	2

Conclusions: At median 5-year follow-up, early-stage breast cancer patients successfully treated with single 20 Gy fraction IORT using disposable balloon electronic brachytherapy demonstrated a low IBTR consistent with published reports.[3] “Unsuitable” patients with positive margins were easily dealt with by re-excision with a small IBTR increase which was not statistically significant. It is recommended that future trials investigate this subset as a primary endpoint with enough statistic power to conclusively answer this question.

References:

1. Correa CC, Harris EE, Leonardi MC, et al. Accelerated Partial Breast Irradiation: Executive Summary for the Update of an ASTRO Evidence-Based Consensus Statement. Pract Radiat Oncol. 2017 Mar-Apr;7(2):73-79.

2. Shaitelman SF, Anderson BM. Arthur DW, et al. Partial Breast Irradiation for Patients With Early-Stage Invasive Breast Cancer or Ductal Carcinoma in Situ: An ASTRO Clinical Practice Guideline. Pract Radiat Oncol. 2024 Mar;14(2):112-132.

3. Vaidya JS, Joseph, JS Tobias, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial); an international, prospective, randomized, non-inferiority phase 3 trial. Lancet 2010 July;376:91-102.